Comprehensive Review

Long-Term Neuropsychological Effects of Opioid Use in Children: A Descriptive Literature Review

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Background: Use of opioids in the management of pain and its consequences in children presents a substantial challenge. A significant concern in pediatric pain management is the long-term neuropsychological consequences of opioids.

Objectives: The authors aim to provide a descriptive review of the current literature surrounding the neuropsychological impact of opioid use in children, along with possible extrapolations from their use in adults and animal models.

Study Design: Systematic review of published literature.

Setting: Various universities in the United States.

Methods: The electronic review for papers published between January 1992 and December 2012 was conducted using Medline/Pubmed, PsychInfo, CINAHL, the Cochrane Library database, and Google Scholar.

Results: Findings assessing pediatric pain patients treated with opioids demonstrated no significant differences in intelligence, behavior, vocabulary, or motor skills. One study reported a decrease in a visuo-constructional ability, which measured higher order executive function. Studies from prenatal illicit opioid exposure found poorer performance on measures of language, verbal ability, mathematics, reading, impulse control, and school readiness skills. The literature from adult prescribed opioid users has mixed results. Some showed impairment in the neuropsychological domains of memory, decision-making, attention, concentration, information processing, psycho-motor speed, visual special skills, and hand-eye coordination, while others found no differences or revealed improved perceptual-cognitive status, possibly due to the removal of pain as a stressor.

Limitations: Very few studies looked into the long term neuropsychological and cognitive effects of the opioids in pediatric population. In an attempt to extrapolate from other groups, this review also included literature from adult patients, prenatal opioid exposure, and animal studies.

Conclusion: Opioid medications have the potential to produce long-lasting neuropsychological side effects. However, given the negative consequences of untreated pain, the potential benefit may offset their risk. More studies are needed to clarify this complex interaction.

Key words: Chronic pain management, infants, children, pediatrics, long term neurocognitive effects, opioid medication

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Pain and its treatment may have effects beyond the normal recovery period, and a substantial number of children suffering from pain would benefit from more effective pain management (1,2). In a scientific workshop by the US Food and Drug Administration, a prominent concern was whether pain medications for adults were equally safe for use in young children. Pediatric pain experts agreed that more short- and long-term clinical data are needed to address the safety and efficacy of opioid pain medications in children (3).

In the past 2 decades, medical advancements have increased the survival rate of prematurely born infants, those with life-threatening diseases and those undergoing surgery as neonates (4). There is greater sensitivity to pain in preterm compared to term-born infants, and constant exposure to pain can result in hypersensitivity (5). These infants often undergo stress, due to severe pain, which can have deleterious effects on their development (6). Untreated pain can negatively influence neonates' generalized stress-arousal systems and effect brain cytoarchitecture and the immune system (7-11). Anand et al (1999) (12) reported that repeated pain in neonatal rat pups may result in altered development of pathways linked to decreased pain threshold during development. This might be attributable to increased plasticity of the neonatal brain, increasing vulnerability to stress disorders and/or anxiety-mediated adult behavior. Similar behavioral changes have been observed during the later childhood of preterm neonates exposed to prolonged periods of neonatal intensive care. Severe pain also has the potential to lessen concentration ability, reducing cognitive performance (13-17). Hence, effective management of pain is a crucial factor in promoting healthy development in this vulnerable population.

As we become more sophisticated to symptom and disease management, more health care clinicians and parents have been willing to provide opioid medications to neonates and children for the treatment of pain (1). In recent years, there has been an increase in the number of pain medications prescribed to children (18), which is concerning given that the overwhelming majority are off label (4). There are differences in the pharmacodynamics and pharmacokinetics of drug metabolism in neonates and children relative to adults. There are obvious differences in size, internal metabolic rate, organ development, and capacity to metabolize and to eliminate drugs (19).

A major concern of pain management in children is the long-term consequences of opioid pain medication usage (1,3). Most markedly, the constantly developing brain and bodies of children make drug effects a major concern in the pediatric population (3,18). In 2006, the American Academy of Pediatrics reversed previous support for the routine use of continuous infusions of morphine or fentanyl for the treatment of pain after surgery or in chronically ventilated preterm neonates due to short-term adverse effects, lack of demonstrated effectiveness for relieving pain, and lack of beneficial long-term outcomes (20). There remains considerable concern that the use of opioid medications may potentially lead to adverse cognitive and psychomotor effects, as there are many opioid receptors in the brain regions which mediate or modulate attention, memory, and learning tasks (21).

Physiologically, heroin exposure decreases birth weight, birth length, and head circumference; with prenatal opiate exposure having a severe impact on infant central and autonomic nervous systems (22). Although the negative cognitive effects of illicit prenatal opioid drug exposure may seem obvious, research has also found equivocal findings regarding the use of opioids in post-natal and adult populations. Here, we provide a descriptive review of the current literature for long-term neuropsychological and cognitive effects of opioid use in pediatric, adult, and animal populations.

Methods

We searched using MEDLINE/ Pubmed, PsycINFO, CINAHL, and the Cochrane Library database for all articles published from January 1992 through December 2012, stemming 20 years. Keywords and phrases included: "pain," "chronic pain," "opiates," "opioid," "cognition," "cognitive impairments," "children," "pediatrics," "infant," "development," "psychological effects," and "neuropsychological." Additional material was obtained by using the Google web and Google Scholar search engines. Three authors (G.J., V.M., S.S.) reviewed all articles. The review was limited to articles focusing on long-term neuropsychological and cognitive effects of prescribed opioid exposure in pediatric and adult patients, prenatal opioid exposure, and animal studies. The reference lists of the identified papers and other publications by their authors were also examined to ensure that all articles meeting criteria were identified. Comparison studies, follow-up studies, cross-sectional comparison studies, randomized control trials, and review articles were assessed. Articles focusing on long-term neurocognitive effects of illicit drug use in adults

were excluded due to the difficulty in differentiating impairments attributable to poly-drug abuse, excessive and unreliable opioid dosing, difference in personality, brain dysfunction, and environmental influences.

RESULTS

Research on long-term neuropsychological and cognitive effects of opioid pain medications for children is limited and summarized in Table 1. Children,

Table 1. *Summary of all studies included in the review.*

Study	Type of Study	Study Groups	Type/ Duration of Opioid Use	Psychological Tests/ Measures	Results/ Implications	Limitations
Neonates and children with opioid exposure						
de Graaf et al (2011)	5 year follow-up of RCT	Morphine-infused vs. placebo	Continuous morphine	Intelligence (RAKIT)[1] Visual Motor Integration (Beery-VMI)[2] Behavior (CBCL)[3] Chronic Pain (CPQ)[4] Health-related Quality of Life (HUI-15)[5]	Poorer visual analysis scores. Heroin impacts visuo-motor & inhibitory skills	Small sample size Potential selection bias Did not assess gross motor development
MacGregor et al (1998)	5 – 6 year follow-up of RCT	Morphine vs. Non-morphine treated children	Neonatal period; Median of 56 hours	Intelligence (WPPSI)[9] Motor development (MABC)[10] Behavior (CBCL)[3]	No significant difference on any scale. Slightly better performance on all scales in morphine group. Short-term use of morphine in neonates causes no harm	Detailed results on subdivisions of each scale were not given
Guerra et al (2011)	18 – 24 month prospective observational follow-up	Infant cardiac surgery patients given sedatives and analgesics	Pre-, intra- & post-operative use of opioids, benzodiazepines & inhalation agents	Developmental measures-(Bayley Scales-BSID II & Bayley III)[6] Adaptive Behavior Assessment System (ABAS)[7]	No association between sedation/ analgesia & mental, motor or vocabulary delays	Two different editions of Bayley scales used- Bayley III does not include language scale. Sample is of cardiac patients-not generalizable. Not all patients received ketamine
Roze et al (2008)	Prospective population-based study	Very pre-term infants	Administration of sedation/ analgesia for more than 7 days	Neuropsychological assessment/intelligence (KABC)[8]	No adverse effects	Power of study not high enough to detect 10% difference in disability rate Limitations imposed by use of propensity score
In-Utero exposure of opioid drugs						
Pulsifer et al (2008)	Cross-sectional comparison study	Prenatal drug-exposed vs. Nondrug-exposed children	Women using cocaine or opiates or both during pregnancy	Cognitive functioning- 6 areas[11] Attention/impulse control (GDS)[12] Visual attention span & sequencing (KCT)[13] Finger & hand dexterity (PPT)[14]	Poorer performance on language, school readiness skills, impulse control, visual attention span/ sequencing. No difference in intelligence, manual dexterity, visual-motor & sustained attention. No effect of type of drug exposure. Implications for academic & behavioral outcomes	Low retention rate at 5 year follow-up reduces generalizability
Ornoy et al (2001)	Comparison study	Raised-at- home children born of heroin-dependent mothers (T1) vs. those adopted (T2) vs. children born to fathers with heroin dependency vs. children with severe environmen-tal deprivation vs. age-matched controls	Heroin-dependency during pregnancy in 2 target groups-T1 & T2	Neurological examination (TPN)[15] Intelligence (WISC-R, 4 sub-tests)[16] Visual-motor maturity (BGT)[17] Standard tests of reading & arithmetic Attention deficits (Conner's)[18] Inattention & hyperactivity (PTT)[19] Behavior (CBCL)[3]	Children of heroin-dependent parents raised at home & those with environmental deprivation had: Poorer scores on intelligence scales, reading & arithmetic High rate of Attention Deficit Hyperactivity Disorder (ADHD) Neurocognitive deficits result from heroin use	High presence of comorbid attention deficit hyperactivity disorder History of poly-drug abuse

Table 1 (cont.). *Summary of all studies included in the review.*

Study	Type of Study	Study Groups	Type/ Duration of Opioid Use	Psychological Tests/ Measures	Results/ Implications	Limitations
de Cubas et al (1993)	Comparison study	20 school age children prenatally exposed to methadone vs. 20 non-exposed children	Prenatal exposure to methadone	Intelligence (SBIS, Form L-M)[20] Social & Emotional development (RATC)[21] Achievement (KABC)[8] Behavioral (CBCL)[3]	No significant difference Methadone exposure associated with: lower IQ greater anxiety, aggression & rejection themed responses helplessness	Moderate alcohol & nicotine use during pregnancy was seen in both groups. With these substances known to cause developmental problems and their potentially compounding effects along with methadone use might have affected results
Bandstra et al (2010)	Review	Prenatal opioid use	Opiates	-	Increased risk of neuro-developmental impairment Home environment plays significant modulating role on outcome	Methodological limitations in most studies. Limited studies on long-term effects of opioid exposure. Problems with sample- High attrition rate, variability of drug-dependent lifestyle
Adult prescription opioid users						
Sjogren et al (2000)	Comparison study	Chronic pain patients treated with oral Opioid vs. healthy volunteers	Long-term oral Opioid treatment on a fixed time schedule and stable daily doses (15-300 mg) > 14 days	Neuropsychological tests: Attention/concentration (CRT)[22] Psychomotor speed (FTT)[23] Working memory (PASAT)[24]	Significantly reduced scores on PASAT, CRT, FTT indicate impaired general adaptation & information processing	Unclear if opioids played a causal role in impaired neuropsychological scores.
Kamboj et al (2005)	Double-blind, placebo-controlled cross over design	Additional immediate - release opioids Vs placebo in patients who are already on sustained – release opioids	Sustained-release opioid & ≤2 doses of immediate-release morphine/day	Neuropsychological tests: Immediate & delayed episodic memory (RBMT)[25] Attention & working memory Everyday attention (TEA)[26] Verbal fluency Complex visual scanning Psychomotor speed (FTT)[23]	Transient anterograde, & retrograde memory impairment. Poorer performance on complex-tracking task. Enhancement of simple-tracking task scores. Effects everyday cognitive functioning	Presence of pain could be a confounding factor
Chapman et al (2002)	Review	Chronic cancer & non-cancer pain patients	Varied	Varied	Possible impairment in cognitive function during initial days of use of opioids. No discerning effects of opioids on different cognitive functions. No consistent trend seen	Chronic cancer & non-cancer pain itself could confound results in most studies reviewed
Jamison et al (2003)	Retrospective data analysis from a multi-site, open-label, crossover study	Low-back pain patients on long-term opioids	Either oxycodone with acetaminophen or transdermal fentanyl for 90 days	Psychomotor speed (DSST)[27] Visual information processing (TMT-Form B)[28]	Improved concentration & hand-eye coordination. Facilitative effect of opioids	Tests performed on multiple sites by unlicensed staff. Practice effect of test taking. No control group. All patients not followed up for 180 days. Patients were not opioid-naiive
Lorenz et al., (1997)	Pre- and Post-treatment comparison and long-term follow-up	Female patients with chronic pain (n = 6)	Long acting morphine with assessment within 14 days and between 1.5 to 3 years	Laser paradigm with measurement of laser and auditory evoked potentials (LEP & AEP) Auditory oddball task to measure reaction time	Improved alertness: LEP & AEP amplitudes (P2 and P300) exhibited weak, yet significant, enlargements. reaction time was slightly reduced. Long-term group did not report any cognitive decline	Small sample size with only female subjects. No objective assessment data for long term group (n=5)

Table 1 (cont.). *Summary of all studies included in the review.*

Study	Type of Study	Study Groups	Type/ Duration of Opioid Use	Psychological Tests/ Measures	Results/ Implications	Limitations
Upadhyay et al (2011)	Cross-sectional comparison study	Prescription opioid-dependent patients vs. Healthy controls	Prescription opioids with diagnosis of Opioid Dependence	Structural Magnetic Resonance Imaging (MRI) Diffusion tensor imaging Resting-state fMRI	Bilateral volumetric loss in amygdala & internal & external capsules. Decrease in functional connectivity in anterior insula, nucleus accumbens & amygdala subdivisions associated with longer duration of opioid intake. Affects regulation of affect & impulse control, reward & motivational function	Pre-existing structural or functional conditions of the brain were not screened for
Animal studies						
McPherson et al (2007)	Prospective follow-up study	Control control vs. Control vehicle (saline-injected) vs. Stress vehicle vs. Control morphine vs. Stress morphine	Twice daily morphine sulfate injections for 5 days (post-natal days 3 –7)	Early growth & development indices Adult neurobehavioral tests	Slowed early growth. Impaired passive-avoidance learning. Neonatal morphine treatment impairs adult cognitive functioning in mice	Caution required when extrapolating from animal studies as: brain development in rats is rapid versus those in infants ratio of size to medicine dose is vastly different in rats versus infants though 6 hours of anesthesia in neonatal rat is approx. equal to a month in human infants
Ma et al (2007)	Comparison study	Morphine vs. Saline injected mice	Varied doses of morphine intraperitoneally injected at various times in 3 experiments	Acquisition & retrieval of memory (Y-maze) Effect of morphine withdrawal (Y-maze)	Morphine impaired acquisition & retrieval of spatial recognition memory. Morphine withdrawal impaired acquisition	
Atici et al (2004)	Comparison study	Morphine vs. Tramadol vs. Saline group	Incremental doses every 10 days over 30 days	Presence & number of red neurons- a histologic marker of apoptosis	Presence of red neurons in morphine & tramadol groups indicating possibility of cerebral dysfunction implicates chronic & incremental use of these drugs	
Boasen et al (2009)	Follow-up study	Untreated vs. Morphine vs. Saline vs. Stress + Morphine vs. Stress + Saline injected mice	From Postnatal day 5 to day 9	Developmental measures Adult behaviors: Elevated plus maze testing Either Morphine Place-Preference Conditioning or Forced-Swim test	Neonatal stress or morphine alone impaired adult Place-Preference Conditioning. Long-lasting behavioral effects in the form of reduced adult arousal hence altered learning implicates morphine	

1. RAKIT- Revisie Amsterdamse Kinder Intelligentie Test (Dutch child intelligence test)
2. Beery-VMI- Beery Buktenica Developmental Test of Visual-Motor Integration
3. CBCL- Child Behavior Checklist
4. CPQ- Chronic Pain Questionnaire (Dutch)
5. HUI-15- Health Utility Index
6. Bayley Scales- Bayley Scales of Infant Development- 2nd edition; Bayley Scales of Infant & Toddler Development- 3rd edition
7. ABAS- Adaptive Behavior Assessment System
8. KABC- Kaufman Assessment Battery for Children
9. WPPSI- Wechsler Preschool & Primary Scale of Intelligence
10. MABC- Movement Assessment Battery for Children
11. 6 areas of cognitive functioning- intelligence, school readiness, language, visual-motor, manual dexterity & attention
12. GDS- Gordon Diagnostic System
13. KCT- Knox Cube Test
14. PPT- Purdue Pegboard Test
15. TPN- Touwen & Prechtl Neurological exam
16. WISC-R- Wechsler Intelligence Scale for Children- Revised
17. BGT- Bender Gestalt Test
18. Conner's Attention Deficit Scale
19. PTT- Pollack Taper Test
20. SBIS (Form L-M)- Stanford-Binet Intelligence Scale
21. RATC- Roberts Apperception Test for Children
22. CRT- Continuous Reaction Time
23. FTT- Finger Tapping Test
24. PASAT- Paced Auditory Serial Addition Task
25. RBMT- Rivermead Behavioral Memory Test
26. TEA- Tests of Everyday Attention
27. DSST- Digit Symbol Substitution Test
28. TMT- Trail Making Test

in general, have been medicated based on generalizations from drug studies on adults. Therefore, research regarding long-term neuropsychological and cognitive effects of opioid use from studies of adults has been included to better extrapolate results to the pediatric population. Animal studies are also relevant because the neurological maturity of human preterm neonates at 24 weeks of gestation is similar to neonatal rat pups (12), with similar milestones in the development of pain systems and demonstrated similar post-natal brain plasticity as that of human premature infant between 24 to 36 weeks gestation (23,24). Thus, pre-natal exposure to illicit use of opioids, studies of chronic opioid use in adult patients treated for pain, and animal studies are reviewed. These findings may all provide insight into possible long-term effects of opioids in children. Table 1 summarizes major studies in each of these categories.

Studies on Neonates and Children

Only 4 studies examining long-term neuropsychological effects of opioids in neonates were identified. de Graaf et al (2011) (25) published a 5 year follow-up of mechanically ventilated neonates who were given routine morphine infusion (49 children) as part of a randomized placebo (41 children) controlled trial. They were tested on intelligence, visual motor integration, behavior, chronic pain, and health-related quality of life. Significant differences in Intelligence Quotient (IQ) scores were found between the morphine group and the placebo group (P = .049). However, once the authors controlled for relevant co-variables, the only significant difference was on an IQ subtest, "visual analysis," which was negatively related to having received morphine and to open-label morphine consumption in the first 28 days. The investigators cautioned towards a more detailed assessment of morphine administered children, as deficits in visual analysis reflect poor visuo-constructional abilities as well as poor inhibitory skills (a higher-order neurocognitive function), which can have long term sequelae.

A similar study provided conflicting results. Mac-Gregor et al (1998) (26) assessed outcome at 5 – 6 years in a cohort of 85 pre-term infants (< 34 weeks of gestation) who were mechanically ventilated and randomly allocated within a controlled clinical trial to receive morphine or non-morphine (pancuronium or 5% dextrose solution) treatment in the neonatal period. Children were assessed using 3 scales: Weschler Preschool and Primary Scale of Intelligence, the Movement Assessment Battery for children, and the Child Behavior checklist. This study found no significant difference in any of the 3 test scales between 2 groups, but there was a trend towards better performance in all 3 tests in morphine group (26). Limitations of this study were that only overall IQ, motor ability, and behavior were analyzed without any details of the subdivisions of each category.

Guerra et al (2011) (27) studied the neurodevelopmental outcomes at 18 – 24 months of age, in a cohort of infants who underwent complex cardiac surgery within 6 weeks of infancy. All patients received sedation and analgesia (opioids, benzodiazepines, and inhalational agents) during peri-operative period. Adaptive Behavior Assessment system and the Bayley Scales of Infant and Toddler Development were used to assess the mental and motor developments. A regression analysis of 95 survivors found no evidence of an association between sedation/analgesia variables and significant mental, motor, or vocabulary delays (27). Similarly, Roze et al (2008) (28) conducted a prospective population-based study of the long-term outcomes of very preterm infants (< 33 weeks of gestation) who received prolonged sedation and/or analgesia. The authors did not find any adverse 5-year neurological outcomes after adjustment for the propensity score in children with prolonged sedation and/or analgesia (28).

Studies on Children with Prenatal Prescribed and Illicit Opioid Exposure

An additional 4 publications were identified that examined long-term neuropsychological effects of pre-natal opioid exposure. Limitations of these studies of significance to this topic include self-report of drug exposure and no control of dose, frequency, and/or extent of drug exposure. Pulsifer et al (2008) (29) assessed cognitive functioning in 5 year olds, comparing drug-exposed to unexposed children. Among those exposed (self-reported and confirmed by urine toxicology screens of mother and infant), 17.7% were exposed to cocaine only, 26.5% were exposed to opioids only, and 55.8% were exposed to both. The drug-exposed group showed poorer performance on measures of language, school readiness skills, impulse control, and visual attention span/sequencing compared to controls. Intelligence, manual dexterity, visual-motor, and sustained attention scores did not significantly differ between groups. Type of prenatal drug exposure did not significantly affect cognitive performance, with no significant differences between the 3 drug groups on measures of intelligence, school readiness, language, visual-motor, manual dexterity, attention span/sequencing, impulse

control, or sustained attention. Lower verbal ability and impaired reading and arithmetic skills were also found in prenatally heroin exposed children at 5 – 12 years of age (30).

In contrast to these studies showing adverse effects of prenatal drug exposure in children, 2 other publications report no long-term negative neuropsychological effects. de Cubas and Field (1993) (31) did not find any cognitive delay at 6 to 13 years of age in children of methadone dependent women. In a review by Bandstra et al (2010) (32), the authors concluded that there were limited reports on the long-term effects of prenatal opioid exposure on post-natal growth and neurodevelopment. The authors emphasized several methodological flaws in the studies reviewed, which limits generalizablility (32).

Studies on Adult Prescribed Opioid Medication Users

Six publications examining long-term neuropsychological effects of opioids prescribed for adults with pain were identified. Sjogren et al (2000) (15) found neuropsychological performance impairment in chronic nonmalignant pain patients who had been receiving extended opioid therapy as compared to healthy volunteers. They measured arousal, vigilance, task concentration, attention division, fluency of motor sequences, perception and movement coordination, motor performance, and short-term memory. Significantly poorer performance was noted on all tests and maintained after retest. As this is a comparison study, the authors could not determine whether there was a causal effect of opioid use on decreased neurocognitive performance. The authors also caution that severe pain may lessen concentration ability.

Kamboj et al (2005) (33) studied the effects of immediate-release morphine (IRM) versus placebo on cognitive functioning in a cross-over design with 14 patients already receiving long-acting opioid therapy for cancer (n = 12) or chronic non-cancer low back pain. They found anterograde and retrograde memory impairment after IRM. There was a decline in delayed recall of verbal information and performance on a complex tracking task (Reitan's trails B). However, performance improved on a simpler tracking task (Reitan's trails A). They concluded that IRM, when taken with a sustained release opioid, leads to transient anterograde and retrograde memory impairments and decreases in 2 target tracking, possibly negatively impacting everyday functioning.

A review article investigating the effects of intermediate and long-term use of opioids on the cognition of chronic cancer and non-cancer pain patients concluded that impairment has been demonstrated in studies that have compared subjects with significant pain with healthy volunteers. However, in both cancer and non-cancer patients with chronic pain, comparisons between those who were taking opioids versus not using opioids failed to show significant cognitive differences (34).

Favorable results of long-term opioid use have been found by Jamison et al (2003) (21), who measured intellectual ability (digit symbol substation test) and visual information processing involving motor speed and attention (trail making test B). They found improvement in chronic pain patients while they were on opioids (21). Lorenz et al (1997) (14) found that opioid-naïve patients (n = 6) with chronic pain of mean 5 year duration, when adequately treated with sustained-release morphine, had improved perceptual-cognitive status within 2 weeks of adequate relief of pain, possibly due to the removal of pain as a stressor. Thus, it is possible that pain influences cognition to a higher degree than opioid medication use. Long-term follow-up (up to 3 years) of 5 of these patients did not show deterioration in cognitive abilities (14).

Upadhyay et al (2010) (18) reported the first study to evaluate potential brain morphology and functional connectivity changes in prescription opioid-dependent patients. They demonstrated significant volumetric changes, white matter tract abnormalities and alterations in functional connectivity in the amygdala, internal and external capsules, anterior insula, and nucleus accumbens (18). The functional connectivity between the amygdala and the inferior orbital frontal cortex and the nucleus accumbens was significantly related to amygdala volume. These relationships may play a pivotal role in mediating motivation, reward, and addictive behavior. The functional connectivity of the amygdala was also significantly correlated with 3 axional paths that project to and from the amygdala. Finally, the integrative aspect of the dependence between functional connectivity and morphological changes supported the notion that prescription opioids affect both specific structures and entire systems that mediate addiction, reward, motivation, awareness, or interoception (18).

Animal Studies

Animal studies suggest potential damaging long-term effects of opioids. McPherson et al (2007)

(35) found that morphine administration in neonatal rats impaired their adult cognitive functioning. Ma et al (2007) (36) reported deficits in spatial recognition memory whereas Atici et al (2004) (37) found an increase in red neuron degeneration in the rat brain, potentially leading to cerebral dysfunction. Boasen et al (2009) (38) tested whether repeated neonatal stress and/or morphine exposure affects early neurodevelopmental or adult mouse behaviors. Neonatal stress or neonatal morphine alone impaired adult mouse place-preference conditioning, but the combination did not. The authors concluded that neonatal morphine reduces adult arousal and neonatal stress exaggerates adult arousal, each to a degree sufficient to alter learning, while the combined impact of these neonatal treatments does not alter adult learning. Basic science has shown that the opioid system modulates neural proliferation in vivo (39). Extrapolating from these data suggests a harmful role of morphine treatment in disturbing neurogenesis of newborn babies which may lead to long-term adverse effects on cognitive functioning.

Discussion

Overall, there is a paucity of human data on long-term neuropsychological and cognitive effects of opioid administration in neonates and children. In the limited studies assessing the effect of opioid use on cognition during the neonatal period, opioids were used only briefly and mainly for surgical interventions or mechanical ventilation (25-27). In these studies, neuropsychological assessments were done 2 to 5 years after exposure (25-28). These studies did not find any differences in intelligence or behavior, nor were there vocabulary or motor delays (25-28). One study did report a significant difference on an IQ subtest, assessing visual analysis, a higher order executive function which can have long-term sequelae, including poor inhibitory skills (25). In children, these skills develop over many years, so follow-up at a later age may reveal additional neuropsychological effects. Moreover, these studies may be limited because of small sample sizes, selection bias, and methodological concerns (Table 1).

Studies examining the potential effects of prenatal exposure to illicit and prescribed opioids assessed a wide variety of neuropsychological performance in children from neonates to adolescents. Moreover, complex social and environmental conditions may influence the functional and behavioral capacities

of these children. Collectively, these studies report poorer performance on measures of language, verbal ability, mathematics, reading, school readiness skills, impulse control, and visual attention span/sequencing compared to controls. However, some did not show any significant differences in intelligence, manual dexterity, visual-motor, and sustained attention scores compared to controls. Studies had small sample sizes and poorly defined comparison groups which make it difficult to control for relevant covariates, including variation in drug purity and dosages, use of multiple substances, co-morbid medical problems, socioeconomic status, unwanted pregnancy, caregiving environment, and other unknown environmental and lifestyle attributes (29,30,32). High attrition rates also complicate many of these investigations.

Most of the present understanding regarding opioid-related cognitive effects stem from adult studies. These studies compared acute and chronic prescription opioid users to controls and also between groups. These diverse studies show impairment in various domains of neuropsychological functioning including verbal, episodic and working memory, decision-making, attention, concentration, information processing, psychomotor speed, visuospatial skills, and hand-eye coordination. Anatomical changes, like volumetric and white matter variations, were also noted. These changes were accompanied by parallel alterations in functional connectivity in various parts of the brain especially the amygdala and its connections in prescription opioid users compared to controls (18). Some studies reported no significant or temporary impairments over time (34,40). Most interestingly, some studies reported that opioid abstinence can help in the recovery of these cognitive impairments (41). Likewise, studies showed opioid-naïve patients with chronic pain, when adequately treated, had improved perceptual-cognitive status, possibly due to the removal of pain as a stressor. This suggests that pain may have a negative influence on cognition to a higher degree than opioid medication use (14,18).

These studies have limitations. In several studies, results were confounded by the lack of controls for intelligence, personality, socioeconomic status, and cultural and education background. Most did not compare the results of neuropsychological and structural assessments with pre-morbid status. Therefore, it is possible that pre-existing structural or functional conditions of these patients may have biased the findings. Methodological flaws along with small sample

sizes and selection bias may have distorted the results of some studies.

Animal studies reflect the same potential damaging effects of opioids. Structural alterations resulting in cerebral dysfunctions and functional impairments may manifest with memory and behavioral changes, which have been noted in rat and mouse models (35,37). Neonatal stress or opioids alone impaired both neurodevelopment and adult mouse behaviors, sufficient to alter learning. However, the combination of pain and opioids did not alter adult learning (38). This rodent data has not been replicated in higher level species such as monkeys (42). Extrapolating from these data could suggest a harmful role of opioid treatment in disturbing the neurogenesis of newborn babies, which may lead to long-term adverse effects on cognitive functioning. Similarly, repetitive pain in newborns may lead to long-term changes in behavior, and some of these changes could be prevented by analgesic therapy. Long-term negative cognitive effects of opioids may depend on whether they are given in the presence or absence of painful stimulation. However, it is important to cautiously interpret these experimental data before extrapolating across species. These animal data are helpful in further exploration and guidance in potential studies if more stringent human studies are undertaken (43).

Conclusion

Based on the publications reviewed, opioid medications have the potential to produce long-lasting neuropsychological and cognitive effects. Whether these findings are merely hints of more significant learning and behavioral problems from opioid exposure during children's crucial developmental stages, with increasing social and academic challenges, requires further longitudinal research. However, when opioids are prescribed to treat pain, the potential benefit may offset their risk. More studies are needed to better clarify these complex interactions and to provide best practice strategies that are evidence based for our pediatric population when long-term opioid treatment is being considered in the treatment plan.

Acknowledgments

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